

Dual effect of disopyramide on atrial and atrioventricular conduction and refractory periods

J. S. BIRKHEAD AND E. M. VAUGHAN WILLIAMS

From the Departments of Cardiology and Pharmacology, Oxford University

Disopyramide has been shown in conditions of cholinergic blockade to have a depressant effect upon sinus node automaticity and the atrial refractoriness. It also prolongs atrioventricular conduction and increases atrioventricular refractoriness. These effects may often be masked in vivo by the anticholinergic effects of the drug.

Disopyramide¹ is an antiarrhythmic compound which is effective against both ventricular and supraventricular arrhythmias (Jennings *et al.*, 1976; Mizgala and Huvell, 1976) and may also be of value in tachyarrhythmias related to the Wolff-Parkinson-White syndrome (Spurrell *et al.*, 1975).

It has been shown *in vitro* to reduce the maximum rate of depolarisation in both atrial (Sekiya and Vaughan Williams, 1963) and ventricular tissues (Yeh *et al.*, 1973) and is a local anaesthetic. It is thus an antiarrhythmic drug of the first class. In addition, it slightly prolongs the duration of the atrial action potential *in vitro* (Sekiya and Vaughan Williams, 1963) and *in vivo* (Edwards *et al.*, 1976) (Class 3 action). A drug possessing membrane stabilising properties on atrial and ventricular tissue might be expected to prolong the functional refractory period. Though such an effect has been shown in the ventricles in man (Spurrell *et al.*, 1975), there has been considerable disagreement concerning the action of this compound upon sinus node, atrial, and atrioventricular nodal function. It has been suggested that the variability of the electrophysiological responses of these tissues to the drug may be the result of an atropine-like action of disopyramide (Sekiya and Vaughan Williams, 1963) which would shorten atrial and atrioventricular nodal conduction time, especially if vagal tone was high, and thus mask the direct depressant effect of the compound.

The present study was undertaken to investigate the effect of intravenously administered disopyramide when the parasympathetic control of the heart had already been antagonised by atropine, in order to allow any direct depressant effect of the com-

pound to become manifest. Thus the relative contribution of the two actions could be assessed.

Patients and methods

Fourteen patients were studied (Table 1). Twelve had clinical or electrocardiological evidence of arrhythmias and the primary investigation was the study of the arrhythmias. One had mild pulmonary stenosis, and underwent right heart catheterisation, and another patient had ischaemic heart disease. All gave informed and written consent to the further procedures described here. None was receiving any cardioactive or other medication, and all were studied in a fasting state.

A quadripolar pacing catheter (USCI 5F) was introduced percutaneously into the right femoral vein and advanced to the high right atrium under fluoroscopic control. The distal pair of electrodes was used to pace the high right atrium at the junction with the superior vena cava. The proximal pair of electrodes recorded a high right atrial electrogram. A second, bipolar, pacing electrode (USCI 5F/6F) was introduced percutaneously via the right femoral vein and advanced under fluoroscopic control through the tricuspid valve to a position suitable for recording the His bundle deflection. The intracardiac potentials were recorded, suitably filtered, together with three surface electrocardiographic leads (Standard leads I, II, III, or V1), using an Elema-Schonander Mingograph 82 at a paper speed of 100 mm s⁻¹. Pacing and programmed stimuli, of 2 ms duration and twice threshold strength, were delivered by a specially-built stimulator, based on the Grass S44 module.

The high right atrium was paced at rates of 110, 130, 150 min⁻¹ (1.8, 2.2, and 2.5 Hz). Sinus node recovery time was measured as the time from the

¹Rythmodan, Roussel.

Table 1

Case No.	Sex	Age (y)	Diagnosis
1	M	51	Sick sinus syndrome
2	M	16	Mild pulmonary stenosis
3	M	50	Coronary artery disease
4	M	50	Paroxysmal atrial tachycardia
5	M	42	Paroxysmal atrial fibrillation, mild mitral stenosis
6	F	60	Sick sinus syndrome
7	F	59	Sick sinus syndrome
8	M	45	Re-entrant atrioventricular nodal tachycardias
9	M	54	Adams-Stokes attacks, right bundle-branch block with normal axis
10	M	20	Normal heart
11	F	42	Paroxysmal atrial tachycardias
12	M	55	Recurrent ventricular fibrillation, coronary artery disease
13	F	18	Lown-Ganong-Levine syndrome
14	F	76	Right bundle-branch block and left axis deviation

last stimulus of a 2 min train at 150 min^{-1} (2.5 Hz) to the onset of the first spontaneous sinus impulse. The refractory periods of the atrium and atrioventricular node were determined during fixed rate pacing by the introduction of premature stimuli (St 2). The fixed driving rate employed was in the range 1.6 to 2.1 Hz (600 to 475 ms RR intervals), and was constant for each patient. Heart rate, sinus node recovery time, atrial and atrioventricular conduction times, and the refractory periods of the atrium and atrioventricular node were measured under basal conditions, and after the intravenous injection of atropine sulphate, 0.025 mg kg^{-1} . Measurements were then repeated after the intravenous injection (over 2 min) of disopyramide 2 mg kg^{-1} .

Measurements were completed within 15 minutes of the end of the injection, at which time plasma concentration would be expected to be within the therapeutic range (Ward and Kinghorn, 1976; Spurrell *et al.*, 1975).

Definitions

R-R: the cycle length of the paced or spontaneous rhythm, in ms.

HRA-LRA: the time in ms from the origin of the high right atrial potential to the origin of the low right atrial potential seen on the His bundle electrogram, representing right atrial conduction time.

LRA-H: the time in ms from the low right atrial potential seen on the His bundle electrogram to the His potential, representing atrioventricular-nodal conduction time.

St1-St2: the time in ms between a pacing stimulus and a premature stimulus.

ERP atrium: the effective refractory period of the atrium is the longest St1-St2 interval that does not

result in atrial depolarisation by St2.

ERP-AVN: the effective refractory period of the atrioventricular node is the longest LRA1-LRA2 interval that does not result in conduction of LRA2 to the bundle of His.

FRP-AVN: the functional refractory period of the atrioventricular node is the shortest H1-H2 interval resulting from two atrial depolarisations.

Results

These are summarised in Tables 2 and 3.

The mean sinus node recovery time was shortened by atropine from 947 ± 321 to 714 ± 167 ms ($P < 0.01$; $n=7$), and the mean heart rate increased from 70 ± 18 to 105 ± 27 beats per min ($P < 0.001$; $n=14$). The mean ERP of the atrium was shortened from 258 ± 31 to 232 ± 33 (NS; $n=9$). The FRP of the atrioventricular node was shortened from 429 ± 68 to 355 ± 38 ms ($P < 0.01$; $n=9$).

All the results reported in the following section refer to the effect of disopyramide 2 mg kg^{-1} in patients who had been pretreated with atropine 0.025 mg kg^{-1} .

The mean sinus node recovery time was prolonged from 714 ± 167 to 826 ± 223 ms ($P < 0.01$; $n=7$). The mean heart rate was reduced from 105 ± 27 to 87 ± 23 per min ($P < 0.001$; $n=14$). The mean ERP of the atrium was increased from 232 ± 33 to 268 ± 43 ms ($P < 0.01$; $n=9$). The LRA-H interval in sinus rhythm was prolonged from 80 ± 15 to 91 ± 16 ms ($P < 0.01$; $n=14$). With high right atrial pacing at 130 min^{-1} (2.2 Hz) the prolongation was more pronounced, being from 78 ± 33 to 148 ± 76 ms ($P < 0.05$; $n=7$). The ERP of the atrioventricular node could only be measured on 2 out of 9 occasions in 7 patients when this was longer than the ERP of the atrium. The FRP of the atrioventricular node was much increased from 355 ± 38 to 423 ± 54 ms ($P < 0.001$; $n=9$). There were small and insignificant changes in intra-atrial and His-Purkinje conduction times.

Table 2 Values for heart rate, sinus node recovery time, and intracardiac conduction time

	Basal	Atropine (0.025 mg/kg)	Disopyramide (2 mg/kg)	
Heart rate	70 ± 18 min	105 ± 27	87 ± 23	$n=14$
Sinus node recovery time	947 ± 321 ms	714 ± 167	826 ± 223	$n=7$
HRA-LRA	39 ± 12 ms	36 ± 8	39 ± 9	$n=8$
LRA-H	92 ± 20 ms	80 ± 15	91 ± 16	$n=14$
	123 ± 34 ms*	$87 \pm 23^*$	$120 \pm 43^*$	$n=7$
	$137 \pm 36^\dagger$ ms	$78 \pm 33^\dagger$	$148 \pm 78^\dagger$	$n=7$
HV	49 ± 7 ms	47 ± 9	50 ± 8	$n=14$

*During high right atrial pacing at 110 min^{-1} .

†During high right atrial pacing at 130 min^{-1} .

Table 3 Effective refractory period of atrium and functional refractory period of atrioventricular node measured in milliseconds

Case No.	Driving rate	ERP of atrium (ms)		Disopyramide	FRP of AVN (ms)		Disopyramide
		Basal	Atropine		Basal	Atropine	
1	600	330	205	220	550	400	450
2	475	275	165	210	375	335	350
3	475	230	250	210	375	290	330
4	500	275	225	300	470	415	470
5	500	230	255	290	415	370	415
6	500	250	285	325	510	345	445
7	600	240	225	270	435	375	500
8*	550	255	240	290	385	340	440
	500	240	240	300	350	330	410
	430	230	240	255	415	370	455
Mean and SEM		258 \pm 31	232 \pm 33 NS	268 \pm 43 P < 0.01	429 \pm 68	355 \pm 38 P < 0.01	423 \pm 54 P < 0.001

*Case 8 was studied at three driving rates

Discussion

Intracellular studies on isolated rabbit atria (Sekiya and Vaughan Williams, 1963) and isolated ventricular fibres (Yeh *et al.*, 1973) of the effect of disopyramide have shown 'membrane stabilising' properties indicating that the drug is an antiarrhythmic agent of the first class (Vaughan Williams, 1975). It is also a local anaesthetic. Sekiya and Vaughan Williams (1963) also showed a prolongation of action potential duration (class 3 action), during intracellular recording on rabbit atria, which has been confirmed in the anaesthetised dog by Edwards *et al.* (1976) recording monophasic action potentials with suction electrodes. The expected findings in man with a compound having the above properties would be a prolongation of atrial, atrioventricular nodal, and ventricular refractoriness. While Spurrell *et al.* (1975) have shown a clear-cut prolongation in the refractory period of the ventricle, there has been considerable variation in the reported effects of disopyramide upon sinus node automaticity, atrial and atrioventricular conduction times, and refractory periods.

Befeler *et al.* (1975) have shown a modest reduction in sinus node recovery time 15 minutes after administration, but which later increased to 146 ms 30 minutes after administration. If this reduction in sinus node recovery time had been the result of the anticholinergic properties of disopyramide then it might have been expected that the sinus rate would also have increased, but the authors state that the basic sinus rate was not altered. In the present study a fall in heart rate has been noted together with a prolongation of the sinus node recovery time, results which are both in accord with *in vitro* studies.

Spurrell *et al.* (1975) found that the disopyramide

produced pronounced prolongation in the effective refractory period of the atrium in 7 patients. On the other hand, Josephson *et al.* (1973) did not see consistent changes; in 24 measurements in 12 patients the atrial effective refractory period was prolonged in 13, shortened in 6, and unchanged in 5. There was a small mean prolongation of 13 ms. Similarly, Befeler *et al.* (1975) did not observe consistent changes, but noted a small mean shortening of the atrial effective refractory period of 30 ms. The present study showed a mean prolongation of atrial effective refractory period from 232 ± 33 to 268 ± 43 ms.

All these apparently conflicting results may be reconciled. After cholinergic blockade with atropine the prolongation of atrial effective refractory period shown in this study is in agreement with the depressant action on conduction reported in studies *in vitro*. It is apparent that *in vivo* the total effect of disopyramide depends upon the degree of vagal tone. If this is high then the anticholinergic action of disopyramide predominates, and the resultant effect is a shortening of the atrial effective refractory period. When vagal action is abolished by atropine then the direct depressant action of disopyramide is shown and a lengthening of atrial effective refractory period is observed.

Variable effects of disopyramide have also been reported on atrioventricular conduction and refractory periods. Josephson *et al.* (1973) found disopyramide shortened the effective refractory period of the atrioventricular node and was without effect on the functional refractory period. Marriott *et al.* (1975) did not find any consistent alteration in the effective refractory period of the atrioventricular node. Befeler *et al.* (1975) also found the effective refractory period of the atrioventricular node to be unchanged after disopyramide but showed a small

increase in the functional refractory period of the atrioventricular node. In the present work, after cholinergic blockade, disopyramide produced a consistent and pronounced prolongation in the functional refractory period of the atrioventricular node of 68 ± 34 ms. There was also a prolongation of the resting LRA-H interval of 11 ± 5 ms, and this prolongation became even more pronounced during high right atrial pacing.

These results suggest that, after cholinergic blockade, disopyramide exerts purely depressant effects upon the sinus node, atrium, and atrioventricular node. It is suggested that the variable results previously shown can be explained by the interaction of the blockade of intrinsic vagal tone and the direct depressant effect of disopyramide.

The question arises, if this interpretation is accepted, whether it could provide a rational basis for the selection of the types of arrhythmia where disopyramide might be appropriate. From the present study it appears that disopyramide should be effective in areas where there is no parasympathetic innervation, such as the His-Purkinje system, ventricular myocardium, and the accessory pathways found in pre-excitation syndromes. This conclusion is in agreement with the empirical clinical findings of several workers.

The anticholinergic effect may also be of value in arrhythmia prophylaxis after myocardial infarction when atrioventricular conduction delay may be a problem (Jennings *et al.*, 1976).

A proviso should be made on the above conclusions. This study observed the effects of disopyramide during the first 15 minutes after administration. No published human work has assessed the effect of disopyramide upon the conduction system for longer than 30 minutes. Edwards *et al.* (1976) have shown in anaesthetised dogs that monophasic action potentials (a measure of the intracellular action potential) recorded with suction electrodes did not achieve maximum prolongation after disopyramide until 30 to 45 minutes after administration. This suggests that previous human studies may have mainly related to the effects of class 1 actions of disopyramide and that the class 3 actions, if of slower onset, may have been underestimated. Amiodarone, a compound having predominantly class 3 actions, has significant antiarrhythmic actions against atrial arrhythmias (Olsson *et al.*, 1973), and thus the class 3 actions possessed by disopyramide may be of similar importance.

Although the present study may explain the inconsistencies noted between previous reports on the basis of the dual action of disopyramide the full electrophysiological effect of disopyramide in-

cluding the class 3 actions has not yet been fully elucidated.

The authors acknowledge the financial assistance of Roussel Ltd., who also provided supplies of disopyramide.

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Requests for reprints to Dr. J. S. Birkhead, General Hospital, Northampton NN1 4QR.